FIG. 3B is a micrograph showing the nuclear staining obtained in the presence of antibodies directed against the T-antigen in IO/LD7/4 cells

FIG. 4A is a graph showing the expression of endothelial marker, Griffonia in the IO/JG2/1 cultures.

FIG. 4B is a graph showing the expression of endothelial marker, ICAM-1 in the IO/JG2/1 cultures.

FIG. 4C is a graph showing the expression of endothelial marker, RECA-1 in the IO/JG2/1 cultures.

FIG. 4D is a graph showing the expression of endothelial marker, OX-18 in the IO/JG2/1 cultures.

FIG. 4E is a graph showing the expression of endothelial marker, OX-6 in the IO/JG2/1 cultures.

FIG. 4F is a graph showing the expression of endothelial marker, OX-17 in the IO/JG2/1 cultures.

FIG. 5A a graphs showing the comparative expression of epithelial marker, cytokeratin in the primary cultures.

FIG. 5B a graphs showing the comparative expression of epithelial marker, RET-PE2 in the primary cultures.

FIG. 5C a graphs showing the comparative expression of epithelial marker, cytokeratin in the IO/LD7/4 clone.

FIG. 5D a graphs showing the comparative expression of epithelial marker, RET-PE2 in the IO/LD7/4 clone.

FIG. 6A is a graph showing the expression of the adhesion molecule ICAM-1 in the IO/LD7/4 clone in the absence of induction by interferon gamma (IFNγ).

FIG. 6B is a graph showing the expression of the adhesion molecule ICAM-1 in the IO/LD7/4 clone in the presence of induction by interferon gamma (IFNγ).

FIG. 6C is a graph showing the expression of the adhesion molecule OX-18 in the IO/LD7/4 clone in the absence of induction by interferon gamma (IFNγ).

FIG. 6D is a graph showing the expression of the adhesion molecule OX-18 in the IO/LD7/4 clone in the presence of induction by interferon gamma (IFNγ).

FIG. 6E is a graph showing the expression of the adhesion molecule OX-6 in the IO/LD7/4 clone in the absence of induction by interferon gamma (IFNγ).

FIG. 6F is a graph showing the expression of the adhesion molecule OX-6 in the IO/LD7/4 clone in the presence of induction by interferon gamma (IFNγ).

FIG. 7A is a bar graph showing, for the IO/LD7/4 cells, the expression of class II I-A histocompatibility antigens (black) and I-E histocompatibility antigens (shaded) in response to IFNγ from 0 to 5 days.

FIG. 7B is a bar graph showing, for the IO/LD7/4 cells, the expression of the adhesion molecules VCAM-1 (shaded bars) ICAM-1 (black bars) in response to IFNγ from 0 to 5 days.

FIG. 8 is a bar graph showing the migration of T-lymphocytes across monolayers consisting of the primary cultures of retinal endothelial cells (REC), retinal pigment epithelial cells (RPE) or the IO/JG2/1 and IO/LD7/4 clones.

FIG. 9 is a set of electron micrographs of IO/LD7/4 cells co-cultivated with dissociated retina; the debris of external segments (ROS) is adjacent to the cells and found in the phagosomes (P).

FIG. 10 is a micrograph showing IO/LD7/4 cells cultivated on slides coated with Matrigel®. The cells show a high contractile capacity, creating stress lines in the matrix.

FIG. 11 is a micrograph showing the hexagonal morphology of the cells obtained after grafting the IO/LD7/4 cells onto the retina of Sprague-Dawley rats.

FIG. 12A is a graph showing the means and standard deviations of the latency times of the pupillary reflexes in response to a light stimulus in rats grafted with primary retinal pigment epithelial cells.

FIG. 12B is a graph showing the means and standard deviations of the latency times of the pupillary reflexes in response to a light stimulus in rats grafted with IO/LD7/4 cells.

FIG. 12C is a graph showing the means and standard deviations of the latency times of the pupillary reflexes in response to a light stimulus in control animals (blank operation)

FIG. 12D is a graph showing the means and standard deviations of the latency times of the pupillary reflexes in response to a light stimulus in r dystrophic RCS rat as a function of age; the mean latency time of a non-dystrophic rat is 0.48 ± 0.04 second; L = left eye and R = right eye.

FIG. 13A is a graph showing the means and standard deviations of the amplitude of the pupillary reflex responses to light in rats grafted with primary retinal pigment epithelial cells.

FIG. 13B is a graph showing the means and standard deviations of the amplitude of the pupillary reflex responses to light in rats grafted with IO/LD7/4 cells.

FIG. 13C s a graph showing the means and standard deviations of the amplitude of the pupillary reflex responses to light in control rats .

FIG. 13D s a graph showing the means and standard deviations of the amplitude of the pupillary reflex responses to light in a dystrophic RCS rat as a function of age. The mean amplitude of response of a non-dystrophic 6-month-old animal is 19.7±5.7%; L = left eye and R = right eye.

FIG. 14 is a bar graph showing the modifications of the mean activity of rats placed in cages with walls of different designs; rats grafted with IO/LD7/4 cells (shaded bars), control rats (blank operation or sham; white bars); blank = plain walls; check = decorated walls.

FIG. 15 is a bar graph showing the number of active units of visual field in the superior colliculus, expressed as a percentage of the number of active units of visual field; the IO/LD7/4 and primary retinal pigment epithelial (RPE) cells are capable of slowing down the loss of visual field in the grafted animals compared with the non-grafted animals (control or sham).

FIGS. 16A-D are representations of recordings showing, on the one hand, a 2-dimensional view of the superior colliculus (FIG. 16A and FIG. 16B, in which C = caudal, M = medial, R = rostral and L = lateral), and on the other hand the maps of the corresponding visual fields of the retina (FIG. 16C and FIG. 16D, in which D = dorsal, N = nasal, V = ventral and T = temporal). The crosses on the map of the colliculus represent the zones for which no recording could be obtained. The dots correspond to the zones for which recordings could be obtained; the left-hand FIGS. (FIG. 16A and FIG. 16C) represent the recordings of a dystrophic 6-month-old rat. The recordings could be made from a single unit (light zone), which is typical of animals of this age. The right-hand FIGS. (FIG. 16B and FIG. 16D) represent the recordings of a rat grafted with IO/LD7/4 cells on the superior temporal retina. It is observed that responses can be obtained from a wide zone of the superior colliculus.

FIGS. 17A-D are a set of graphs showing some of the differences relating to the histological characteristics of the retinas of rats grafted with primary retinal pigment epithelial (RPE) cells or IO/LD7/4 cells. The number of nuclei in the outer nuclear layer is shown in FIG. 17A. The

number of nuclei in the inner nuclear layer is shown in FIG. 17B. The depth of the outer plexiform layer in μm is shown in FIG. 17C. The relative zone (%) of retinas saved by grafting is shown in FIG. 17D.

FIG. 18 is an identification of the deposit of the retinal pigment epithelial cells with extended life-span called IO/LD7/4 on 18th April 1996 in the Collection Nationale de Cultures de Micro-organismes (CNCM) held by the Institut Pasteur, 28 rue de Docteur Roux, 75724 PARIS CEDEX 15, under the identification no. I-1694. The indications in section B states (in French):

> With regard to the nominations in which a European patent is applied for, until the publication of the mention of the grant of the European patent or until the date on which the application shall be refused or withdrawn or shall be deemed to be withdrawn, a sample of the deposited microorganism shall be available only by the issue of a sample to an expert nominated by the requester (Rule 28.4) of the EPC).

Figure 19 is an identification of the deposit of the retinal endothelial cells with extended life-span called IO/JG2/1 on 18th April 1996 in the Collection Nationale de Cultures de Micro-organismes held by the Institut Pasteur, 28 rue de Docteur Roux, 75724 PARIS CEDEX 15, under the identification no. I-1695. The indications in section B states (in French):

> With regard to the nominations in which a European patent is applied for, until the publication of the mention of the grant of the European patent or until the date on which the application shall be refused or withdrawn or shall be deemed to be withdrawn, a sample of the deposited microorganism shall be available only by the issue of a sample to an expert nominated by the requester (Rule 28.4) of the EPC).

FIGS. 20 A-C are a pictograph and a set of graphs showing the head tracking in RCS dystrophic (dys) and non-dystrophic rats (con) at 8 weeks (8w; FIG. 20B) and 50 weeks of age (50w; FIG. 20C). The ordinate is a measure of time spent tracking to the revolving drum (FIG. 20A).

FIG. 21 is a graph showing the tracking behavior in dystrophic RCS rats to stripes of different width. The shams perform near baseline. The cell transplanted rats show significant spared performance.

FIG. 22 is a set of recordings of elevation of luminance over baseline in a set of animals. Each record shows responses at points 200 μm apart across the superior colliculus (dorsal retinal representation above, temporal to left). Unshaded show responses equal to or less than 2.0

candela/m^2; light shading 2.1-2.9 and dark shading >2.9. Animals were tested at 5 months post operative. As can be seen, there is a small sham effect around the injection site, but significantly greater preservation after cell grafting.

FIG. 23 A-B are a set of graphs showing the head tracking after human cell line grafts at 7 weeks (FIG. 23A) and 14 weeks of age (FIG. 23B). Note that the cell transplanted dystrophic rats (cells) perform much like non-dystrophics (congenic) by 10-11 weeks (FIG. 23B) post-transplantation and are significantly improved over sham-injected rats.

FIG. 24 is a set of recordings showing the threshold responses (details as in FIG. 22) recorded 12 weeks post-operative. Here the control was a non-dystrophic that received a graft. The sham injected animal shows evidence of remaining responsiveness seen in unoperated dystrophics around the edge of the superior colliculus. The 2 transplanted animals are examples showing substantially improved responsivenes.

FIG. 25 A-B are a set of photographs. FIG. 25A shows an aspect of the subcutaneous graft on cryostat section without any immunohistochemical treatment. The yellow/brown color is restricted to the graft zone (hRPE clone 7, 3 weeks post-implantation. Bright field, x80). FIG. 25B shows a field of the same section at high magnification. The coloration is intracytoplasmic and present in the majority of the cells (Bright field, x320).

FIG. 26 A-B are a set of photographs. FIG. 26A is a hematoxylin and eosin stain of hRPE clone 7, 3 weeks following subcutaneous post-implantation in the flank of a nude mouse (Bright field, x40). FIG. 26B is a hematoxylin and eosin stain at high magnification of the same section. The colored cells show a normal structure of the nucleus. The graft is infiltrated by cells bearing elongated nuclei, probably fibroblasts (Bright field, x800).

FIG. 27 A-B are a set of photographs showing Schmorl staining. FIG. 27A is a Schmorl stain of hRPE clone 7, 3 weeks following subcutaneous post-implantation in the flank of a nude mouse. The reaction with lipofuscins and/or melanin produce a blue/green staining of the cells within the graft site (Bright field, x160). FIG. 27B is a Schmorl stain of hRPE clone 7, 15 weeks following subcutaneous implantation. A few green/black cells are found at the graft site (Bright field, x160).

FIG. 28 A-F are an analysis of primary human RPE cells and human RPE cells with extended life-span. FIG. 28A and FIG. 28B are a set of phase contrast micrographs of (FIG. 28A) contact-inhibited monolayer of primary cultured human donor RPE cells 10

days after seeding and (FIG. 28B) of human clone hRPE7 cells derived from culture depicted in A (scale bars =100 μm). Both cultures exhibit cobblestone morphology characteristic of RPE cells. FIG. 28C shows the immunocytochemical detection by epifluorescence microscopy of SV40 large T antigen showing correct nuclear expression (scale bar = 20 μm). FIG. 28D shows the immunocytochemical detection by confocal scanning laser microscopy (projected images) of junctional protein ZO-1 showing an almost continuous pattern of peripheral staining (scale bar = 20 μm). FIG. 28E shows the immunocytochemical detection of the RPE cytokeratins 8 and 18. FIG. 28F is an overlay of images depicted in immunomicrographs D and E plus an additional bisbenzimide DNA stain (blue) to highlight the cell nuclei (scale bar = 20 μm).

FIGS 29 A-C is a representation of head tracking to high contrast square-wave gratings. FIG. 29A is a photograph of head tracking apparatus showing RCS rat in holding chamber and rotating drum lined with square-wave grating. FIG. 29B shows the total amount of time spent tracking a moving square-wave grating in seconds over a period of 4 minutes after 10 weeks post-transplant. (FIG. 29C) Head tracking 20 weeks post-transplantation. Error bars represent s.e.m. *$p<0.01$ represents a significant difference as compared to both Sham and Dystrophic groups. $^{+}p<0.05$ represents a significant difference as compared to the hRPE7 group.

FIGS 30 A-E is a set of recordings showing the threshold light sensitivity maps of congenic, dystrophic, hRPE7 transplanted and sham operated RCS rats. RCS rats were divided into 4 groups: (FIG. 30A) normal (3 non-dystrophic rats); (FIG. 30B) no treatment (6 dystrophic rats); (FIG. 30C) hRPE7 cells injected into one eye (5 dystrophic rats); and (FIG. 30D) sham injected (5 dystrophic rats). Schematic representation of a dorsal view of the superior colliculus showing respective thresholds for 76 individual recording sites (color coded squares). A log scale of thresholds measured in candela/m^2 is shown. To test efficacy of hRPE7 grafts versus sham injected animals, significance was determined at each of the 76 points using a randomization test. An area of significantly improved visual function was recorded for the hRPE7 transplanted animals as shown in (FIG. 30E). The corresponding topological representation of the retina onto the superior colliculus is indicated by the letters D (dorsal), V (ventral), N (nasal), and T (temporal). The arrow represents the grafted quadrant.

FIGS. 31A-C are a set of photographs showing anatomical changes in the photoreceptor cell layer following transplantation of hRPE7 in RCS rats. Sections of the retina from (FIG. 31A) a 6-month-old non-dystrophic RCS rat showing full outer nuclear layer thickness. (FIG. 31B) Sham operated RCS rat 5 months post operation showing complete ablation of the outer nuclear layer. (FIG. 31C) hRPE7 transplanted RCS rat 5 months post graft demonstrating significant preservation of the outer nuclear layer. Sections were stained with cresyl violet. GC: ganglion cell layer. INL: inner nuclear layer. ONL: outer nuclear layer. RPE: retinal pigment epithelial cell layer. Scale bar = 25 μm. Panel (FIG. 31A) is also stained with RT-97 anti-heavy neurofilament antibody.

FIGS. 32 A-B are a set of bar graphs showing an assessment of visual function in RCS rats with the hRPE cell line 7 (passages 14 and21) as compared to those with ARPE-19. The results are obtained from a visual stimulus, which moves in an anti-clockwise direction, which viewed from the right eye is a temporal to nasal direction. All transplants were placed in the superior temporal retina of the right eye. Data represent the total time spent head tracking. Experimental groups: Con: non-dystrophic RCS rats (n=10), Dys: un-treated dystrophic RCS rats (n=10), Sham: dystrophic RCS rats received injection of 1 μl cell culture medium (used for hREP7; n=8). H1RPE7p14: hRPE7 at passage 14 injected into dystrophic RCS rats (n=10), H1RPE7p21: hRPE7 at passage 21 injected into dystrophic RCS rats (n=7), ARPE-19p22: ARPE-19 at passage 22 injected into dystrophic RCS rats (n=5). FIG. 32A shows, for comparison, data of each experimental group were pooled over all square wave gratings (0.125, 0.25 and 0.5 cycles/degree). A significant difference ($p<0.01$) is apparent between the groups which either received cell grafts or remained untreated (sham, dystrophics). ARPE-19 clearly shows a therapeutic effect which comes close to hRPE7p21. FIG. 32 B shows the total time spent head tracking at 0.125 cycles/° and 0.25cycles/° grating stimulus. While congenic animals were also able to track a grating of 0.5cycles/degree none of the other groups (including transplanted groups) were able to do so.

Please replace the paragraph on page 26 begining at line 13 with the following re-written paragraph:

In the majority of sections, the epithelial cell layer was a single layer (monolayer), but a multilayer was observed in certain regions. When the blocks were sectioned